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Photoinduced Oxygenation of Rotenoids. I. Ring Contraction of Dehydrorotenone to Coumarono-chromone*

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When dehydrorotenone (Ia) was photochemically oxygenated in pyridine, a new compound was separated besides rotenonone (IVa). This compound was identified as a coumarono-chromone type one (IIa) from physical data and a chemical evidence. This result demonstrates that a ring contraction of chromeno-chromone to coumarono-chromone occurred during the photoinduced oxygenation.

In earlier publications,¹⁾ it was reported that rotenone (III) was converted into dehydrorotenone (Ia) and rotenonone (IVa) when exposed to air in alcoholic alkaline solution. Recently, Suginome, Yonezawa and Masamune^{2a)} indicated that the irradiation of dehydrorotenone (Ia) in dioxane-ethanol mixture containing sodium borohydride affords rotenonone (IVa) as the major product, whereas the irradiation in the absence of sodium borohydride produced no isolable IVa. The reaction is thought to proceed by way of secondary hydroperoxides formed by the attack of oxygen at methylene group (position 6) of dehydrorotenone.^{2a, b)} The roles of sodium borohydride in the reaction would be to prohibit some of the side reactions and to destroy these hydroperoxides immediately.^{2a)}

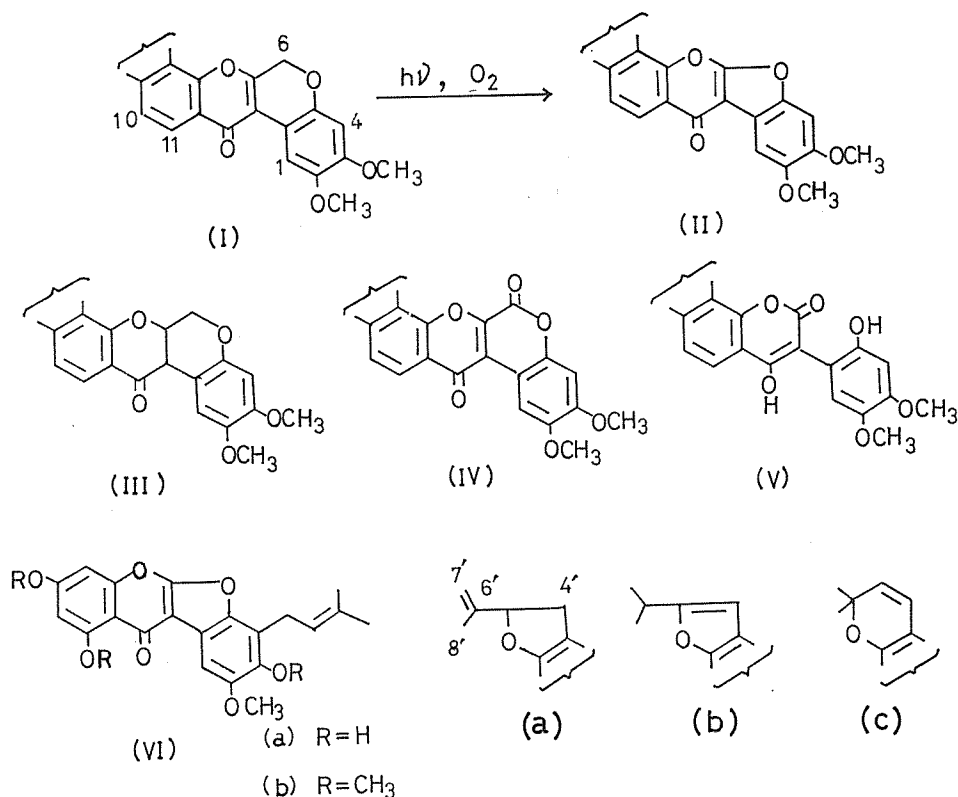
Our interest was directed to the further degradation during the process of photo-oxygenation of dehydrorotenone (Ia). From the irradiated products of dehydrorotenone in pyridine, we have separated a new compound which was elucidated as coumarono-chromone type compound (IIa).

A pyridine solution (2%) of dehydrorotenone (Ia) was irradiated with high-pressure mercury lamp at 42° for 3 hr under the bubbling of oxygen. During the reaction, small amounts of carbon dioxide gas was detected and trapped in barium hydroxide solution. The reaction mixture was cooled overnight and rotenonone (IVa) was isolated, m.p. 297–298°, in 25% yield. The remaining substances were separated into neutral, phenolic and acidic fractions in usual way. On the thin layer chromatograms of the neutral fraction, rotenonone (IVa) and two unknown materials were detected. Subsequently, the neutral fraction was subjected to the separation into its components by the column chromatography over silica gel. The earlier fractions gave rotenonone (IVa) and unaltered dehydrorotenone, and then light brown material was obtained. The yield of this substance which is slightly soluble in common organic solvents was about 3% of consumed dehydrorotenone.

* For preliminary communication on this work, see M. Chubachi and M. Hamada, *Tetrahedron Letters*, **1971**, 3537

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The compound has m.p. 251–252° and $[\alpha]_D^{25} -55^\circ$ ($c=0.17$, CHCl₃). The analytical values and its mol. wt. (378 from mass spectrum) agreed with the formula C₂₂H₁₈O₆. Ultraviolet maxima in ethanol appeared at 236, 259, 289 and 315 nm; infrared (KBr) showed at 1654, 1633, 1617 and 1593 cm⁻¹. On the basis of above data and the following evidences, we formulated the structure of the compound as IIa, being 1,2-dihydro-2-isopropenyl-8, 9-dimethoxy-benzofurano [2,3-b] furo [2,3-h] [1] benzopyran-6-one.

The relative positions of the carbonyl bands in compound IIa ($\nu_{CO}=1654$ cm⁻¹), IIb ($\nu_{CO}=1648$ cm⁻¹) and dehydrorotenone ($\nu_{CO}=1633$ cm⁻¹) suggested that compound IIa and IIb contained a carbonyl group of the chromone type, such as lisetin (VIa) and its derivatives ($\nu_{CO}=1650$ cm⁻¹~1655 cm⁻¹),³⁾ and ultraviolet absorption bands of compound IIa and IIb were also similar to that of lisetin. The nmr absorption bands of compound IIa in (CD₃)₂SO at 8.21 and 6.11 belong to a methyl group and to the two methoxyl groups, respectively. Since 2.47 and 2.66 peaks are singlets, they are assigned to the protons of *para* positions corresponding to those at positions 1 and 4 of dehydrorotenone (Ia), respectively;* and 3.10 and 1.94 (d, $J=8.8$ Hz) peaks are attributed to *ortho* protons corresponding to those at position 10 and 11. The 6', 7'-olefinic linkage in rotenone (IIIa) shifted readily by acid treatment to give the ben-

* For ease of comparison of the chemical shifts of corresponding protons, the formulae of compound IIa, b have been numbered to correspond with the usual convention for rotenone.

zofuran ring such as IIIb.⁴⁾ By the similar treatment of compound IIa with conc. H_2SO_4 , a compound IIb was obtained, m.p. 214–215°, $\text{C}_{22}\text{H}_{18}\text{O}_6$ ($M^+ 378$) and $[\alpha]_D \pm 0^\circ$. The all peaks in nmr spectrum of compound IIb in CDCl_3 were easily assigned⁵⁾ (Fig. 1). From the above results, the compound is an isomer of IIa. Therefore, it is evident that the photoproduct IIa has the structure which was not oxidized either at dihydrofuran ring or isopropenyl moiety in dehydrorotenone (Ia).

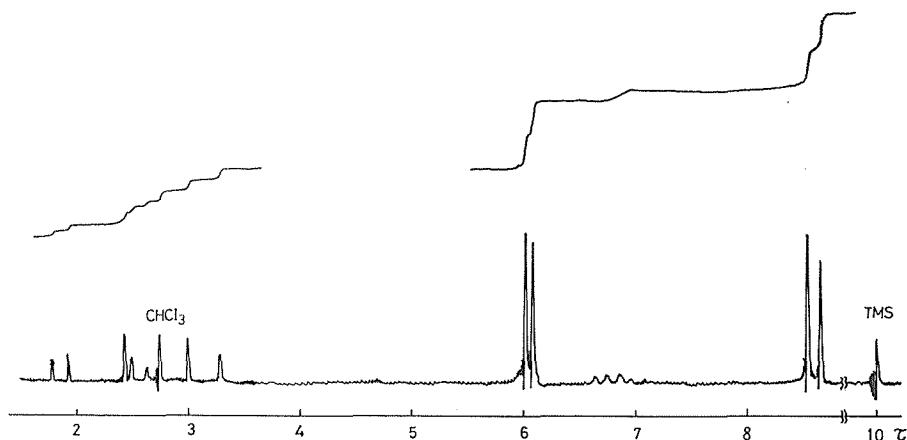


Fig. 1. NMR Spectrum of Compound IIb.

Furthermore, the structure of compound IIa provided an acceptable interpretation of the unusual chemical shift of the proton associated with the low field singlets in the nmr spectra of compound IIa (H_1 , τ 2.47) and IIb (H_1 , τ 2.45). The deshielding of the proton in position 1 of IIa and IIb is completely analogous to the corresponding deshielding shown by the protons in position 1 in dehydrorotenoids,⁶⁾ such as dehydrodeguelin (Ic; H_1 , τ 1.60) and dehydroisorotenone (Ib; H_1 , τ 1.67), and by the proton in position 6' in lisetin trimethyl ether (VIb; H_6 , τ 2.42).³⁾ The magnitude of chemical

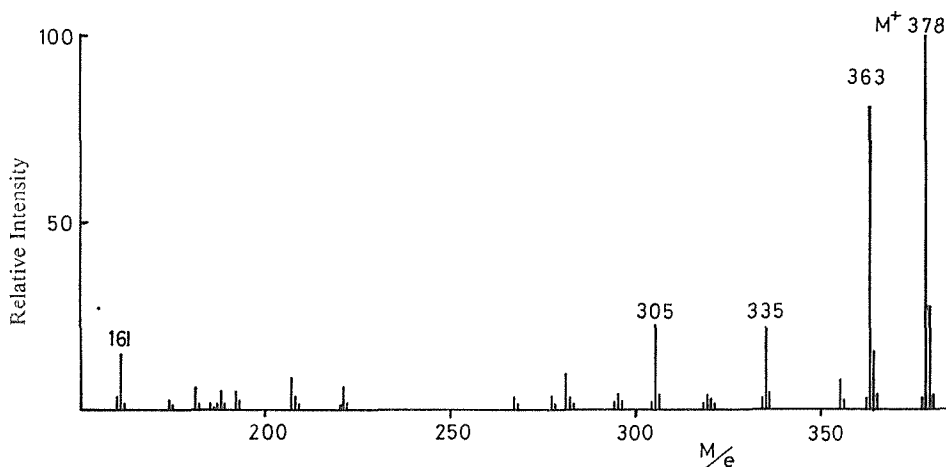


Fig. 2. Mass Spectrum of Compound IIa.

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shifts of protons in position 1 of compound IIa and IIb, as compared with VI and Ib, indicates that the compound IIa has the structure whose skeleton is similar to lisetin. Figure 2 showed the mass spectrum of IIa. The spectrum showed a strong molecular ion peak at m/e 378 and the peak by the predominant fragmentation was the ion at m/e 363 due to loss of methyl radical from the molecular ion. Among the other peaks whose relative abundances were small, the ion at m/e 335, 305 and 161 were also assigned. Cracking pattern of major peaks mentioned above is illustrated in Fig. 3. The structure of coumarono-chromone type presented as IIa is also consistent with those assignments.

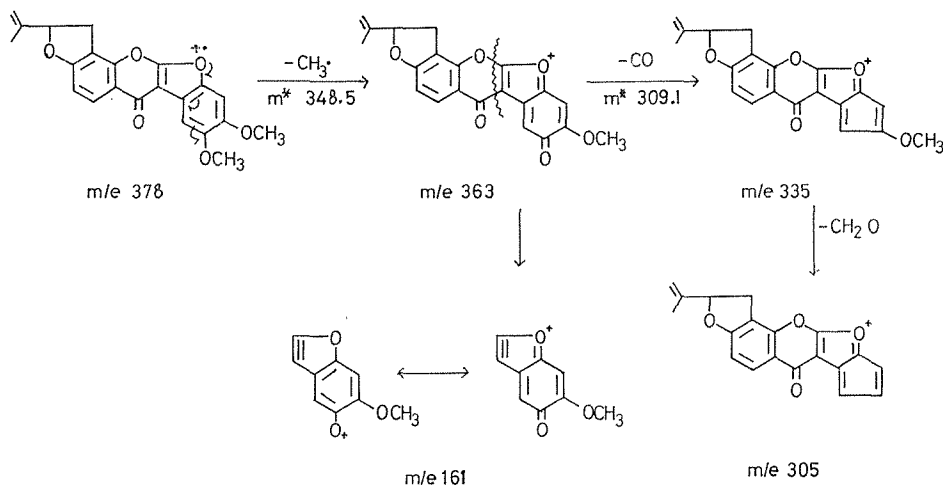


Fig. 3. Mass Fragmentation Mechanism.

An additional support for the structure of IIa is provided by a chemical evidence. The hydrolysis of compound IIb in KOH solution gave 4-hydroxycoumarin (Vb), m.p. 253–254°. The structure of Vb was elucidated by elemental analysis ($C_{22}H_{20}O_7$), infrared and ultraviolet spectroscopic data (ν_{dioxan} 1720 cm^{-1} ($C=O$), λ_{max} 238, 253, 261 and 326 m μ). Falshaw, Ollis, Moore and Magnus³⁾ indicated that the formation of the 4-hydroxycoumarin by alkaline hydrolysis may be useful in the recognition of the type of coumarono-chromone.

From the fact that compound IIa was photochemically produced from dehydrorotenone (Ia), it was proved that chromeno-chromone structure was converted to coumarono-chromone structure by the ring contraction. In the first step of the photo-oxygenation under the present condition, secondary hydroperoxides at position 6 in Ia would be formed as Sugimoto *et al.*^{2a)} indicated. Under basic conditions such as pyridine solution, these hydroperoxides may be predominantly decomposed with the formation of carbonyl (IVa).⁷⁾ Although details of the ring contraction of Ia to IIa were obscure, a portion of the secondary hydroperoxides may decompose to give IIa through β -fission process, accompanying the generation of CO_2 from the carbon of position 6.*

* The irradiation of dehydrorotenone-6- ^{14}C and dehydrorotenone-6a- ^{14}C is under investigation.

Furthermore, the ring contraction of chromeno-chromone to coumarono-chromone is very interesting in connection with a proposal presented by Falshaw, Ollis and his collaborators⁸⁾ in which lisetin might be formed by bio-oxidative transformation of isoflavones that is a precursor in the biosynthesis of rotenone.⁹⁾

EXPERIMENTAL

All m.ps were measured on a hot-stage microscope and uncorrected. Infrared spectra were taken on a Perkin-Elmer 221 or JASCO Model IR-S spectrophotometer; nmr spectra were taken on a JNM-3H-60 spectrometer and chemical shifts are recorded on the τ scale, relative to internal tetramethylsilane. The optical rotations were measured on a Perkin-Elmer 141 polarimeter. Mass spectra were determined at 70eV on a Shimadzu-LKB 9000. The irradiation was carried out with a DHB-400 (DAIKO Co. Ltd.).

Separations by column chromatography were carried out using Wakogel C-200 silica gel. Thin layer chromatograms were developed on silica gel spot film (20×5 cm, 0.25 mm thickness, Tokyo Kasei Co.) with benzene-methanol (50:2) or chloroform-ether (95:5), and were examined under uv illumination and by spraying with 1% KMnO_4 aq. solution. When benzene-methanol solvent system was used and spots were detected with uv light; rotenonone ($R_f=0.78$, yellow); dehydrorotenone ($R_f=0.70$, brown); compound IIa ($R_f=0.57$, blue).

Preparation of dehydrorotenone (Ia)¹⁰⁾

Rotenone (Aldrich Corp., 20 g) and anhydrous sodium acetate (50 g) were dissolved in ethanol (5000 ml). To the solution boiled on the water bath, iodine (16 g) in ethanol (130 ml) was added slowly from the dropping funnel. The reaction mixture was cooled, and the precipitate was collected. Crystallization from CHCl_3 -MeOH gave dehydrorotenone (12 g) as yellow needles, m.p. 217–218°, ν_{max} (KBr) 1633 cm^{-1} (C=O).

Photo-oxygenation of dehydrorotenone and isolation of the products

Dehydrorotenone (3.0 g) was dissolved in pyridine (150 ml) and the solution in a Pyrex flask was irradiated externally with a 400 W high-pressure mercury lamp at 42° for 3 hr under the bubbling of oxygen. Carbon dioxide generated during the irradiation was precipitated as barium carbonate which was collected by filtration, dried and weighed (18 mg).

Rotenonone (IVa). The reaction mixture was cooled overnight. The precipitate was collected and crystallized from glacial acetic acid as yellow needles, m.p. 297–298° (25% yield). The melting point was not depressed when mixed with authentic specimen which was prepared by the method of Takei.¹¹⁾ The substance was definitely identified as rotenonone by ir and uv spectral and cochromatographic comparison.

Coumarono-chromone (IIa). A large portion of pyridine in the above solution was removed by distillation. After the solution was cooled overnight, unaltered dehydrorotenone precipitated was filtered off. Water (150 ml) was added to the filtrate and the solution was acidified with acetic acid and then extracted with ether. The ether solution

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was successively extracted with 5% sodium bicarbonate and 3% sodium hydroxide solution and then washed with water and dried over MgSO_4 . Yields of acidic and phenolic fraction were 90 mg and 80 mg, respectively. After the evaporation of the ether, the residue was chromatographed using benzene-chloroform-methanol (500:150:0.5 v/v) mixtures as eluting solvent. The earlier fractions gave rotenonone and dehydrorotenone, and then light brown material was obtained. Crystallization of the substance from ethanol gave coumarono-chromone (IIa), m.p. 251–252° (about 3% yield), $[\alpha]_D -55^\circ$ ($c=0.17$, CHCl_3). λ_{\max} (EtOH) 236 (ϵ 26,400), 259 (29,000), 289 (24,900) and 315 (infl.) (11,500) nm, ν_{\max} (KBr) 1654 (C=O), 1633, 1617 and 1593 cm^{-1} ; nmr ($(\text{CD}_3)_2\text{SO}$) τ 8.21 (1H, s, CH_3), 6.11 (6H, s, $2\text{CH}_3\text{O}$), 2.47 (1H, s, 1-H), 2.66 (1H, s, 4-H), 3.01 (1H, d, 10-H, $J=8.8$ Hz) and 1.94 (1H, d, 11-H, $J=8.8$ Hz); M^+378 (mass spectroscopy); Anal. Calcd. for $\text{C}_{22}\text{H}_{18}\text{O}_6$: C, 69.83; H, 4.80. Found: C, 69.66; H, 4.75.

Acid-catalyzed isomerization of IIa. A mixture of compound IIa (100 mg), glacial acetic acid (2 ml), and concd. sulfuric acid (3 ml) was warmed to 65° for 1 hr. The yellow solution obtained was poured into water (30 ml) and the solid collected was crystallized from chloroform-methanol, giving compound IIb as white prisms, m.p. 217–218°, $[\alpha]_D \pm 0^\circ$ ($c=0.15$, CHCl_3); λ_{\max} (EtOH) 246 (ϵ 41,380), 293 (15,400), 302 (15,400) and 320 (infl.) (8,370) nm, ν_{\max} (KBr) 1648 (C=O), 1625 and 1578 cm^{-1} ; nmr (CDCl_3) 8.61 (6H, d, 2CH_3 , $J=6.9$ Hz), 6.87 (1H, m, 6'-H, $J=6.9$ Hz), 6.04 and 6.09 (6H, s, $2\text{CH}_3\text{O}$), 2.45 (1H, s, 1-H), 3.01 (1H, s, 4-H), 2.59 (1H, d, 10-H, $J=9.0$ Hz), 1.87 (1H, d, 11-H, $J=9.0$ Hz) and 3.30 (1H, s, 4'-H); M^+378 (mass spectroscopy); Anal. Calcd. for $\text{C}_{22}\text{H}_{18}\text{O}_6$: C, 69.83; H, 4.80. Found: C, 69.63; H, 4.74.

Alkaline hydrolysis of IIb. A mixture of compound IIb (110 mg), 10% KOH aq. solution (10 ml) and methanol (25 ml) was heated under nitrogen atmosphere on a steam bath for 2 hr. After cooling, the solution was acidified with 2 N HCl and extracted with ether. The extract, after being washed with water and dried with MgSO_4 , yields 4-hydroxy coumarin (Vb; 78 mg) as brown needles, m.p. 253–254°, from aqueous ethanol. λ_{\max} (EtOH), 238 (ϵ 41,900), 253 (25,930), 261 (25,190) and 326 (16,030) nm; ν_{\max} (dioxane) 1720 cm^{-1} (C=O); Anal. Calcd. for $\text{C}_{22}\text{H}_{20}\text{O}_7$: C, 66.66; H, 5.09. Found: C, 66.55; H, 5.03.

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